REMARKS

Claims 76-98 are pending in the present application. Claims 1-75 were previously canceled. In the present Office Action, the Examiner rejected Claims 76-98 as allegedly lacking enablement under 35 U.S.C. §112 paragraph 1, and as allegedly being obvious under 35 U.S.C. §103(a) in view of U.S. patent No. 5,650,135 (hereinafter, "the '135 patent"), U.S. Patent No.: 6,180,084 (hereinafter, "the '084 patent"), and U.S. Patent No.: 6,087,476 (hereinafter, "the '476 patent).

I. Claims 87-91 Are Rejected Under 35 U.S.C. §112(2)

The Examiner rejects Claims 87-91 as being indefinite. In particular, the Examiner states, "The recitation 'illumination domain comprises a luciferin protein' in claim 87, lines 5-6 is ambiguous and indefinite. It is unclear how would the illumination domain comprises a luciferin reagent and the imaging agent is also luciferin. It is unclear how can the light generating moiety and its substrate are the same." Office Action, page 2. The Applicants now amend Claim 87 and replace "illumination domain comprises a luciferin protein" with "illumination domain comprises a luciferase protein." As such, the illumination domain and imaging reagent are no longer identical. The Applicants request that this rejection be withdrawn.

II. New Claims 76-98 Do Not Constitute New Matter

The Examiner rejects Claims 76-98 under 35 U.S.C. § 112 (1) as containing subject matter which was allegedly not described in the specification. Office Action, page 2. In particular, the Examiner states, "The phrases 'imaging agent' and 'wherein said cells possess or are suspected of possessing polypeptides comprising RGD motifs' claimed in claims 76, 80, 87 and 92, lines 1-3, the phrase 'ex vivo' claimed in claims 77, 81, 88, and 93, lines 1-2 and the phrase 'cells comprise tumor cells' claimed in claims 78, 85, 89 and 94 represent a departure from the specification and the claims as originally filed.'" Office Action, page 2. In addition, the Examiner states "This is a New Matter rejection." Office Action, page 2. The Applicants respectfully disagree.

The phrase "imaging agent" is described in the Specification. For example, "imaging agent" is described in the Specification, among other locations, at page 8, lines 11-22 (describing the technique of bioluminescence imaging with imaging agents); at page 14, lines 10-15 (describing chimeric (*e.g.,* recombinant) molecules of the present invention as comprising a flurorescent, bioluminescent or chemiluminescent polypeptide, wherein "the polypeptides include enzymes that act on a specific reagent to generate a molecule that can be imaged (*e.g.,* luciferase reacting with luciferin *in situ*)"); at page 18, lines 23-31, page 19, lines 1-3 (describing the technique of *in vivo* bioluminescent imaging with imaging agents), and at Example 1 (describing *in vitro* and *in vivo* experiments involving angiogenic vasculature targeting with imaging agents)).

The phrase "wherein said cells possess or are suspected of possessing polypeptides comprising RGD motifs" is described in the Specification. For example, the phrase "wherein said cells possess or are suspected of possessing polypeptides comprising RGD motifs" is described in the Specification, among other locations, at Example 1 (describing the use of an embodiment of the present invention with cells possessing or suspected of possessing polypeptides comprising RGD motifs (*e.g.,* cultured MDA-435 cells; orthotopic mammary tumor cells)).

The phrase "cells comprise tumor cells" is described in the Specification. For example, the phrase "cells comprise tumor cells" is described in the Specification, among other locations, at Example 1 (describing the addition of an embodiment of the present invention into a nude mouse with an orthotopic mammory tumor).

As such, the phrases objected to by the Examiner are described in the Specification and do not constitute New Matter. The Applicants request these rejections be withdrawn.

The phrase "ex vivo" is also described in the Specification. However, in order to expedite prosecution, Claims 77, 81, 88, and 93 are now canceled. The Applicants reserve the right to prosecute these or similar claims in the future. As such, the rejection of Claims 77, 81, 88 and 93 regarding the term "ex vivo" are rendered moot.

III. New Claims 76-98 Are Enabled

A. The Examiner's Enablement Admission

The Examiner admits the following embodiment is enabled within the Specification: "A method for *in situ* or *in vivo* imaging of a tumor neovasculature in an individual comprising administration a chimeric polypeptide wherein the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1." Office Action, page 3 (hereinafter the "Examiner's Enablement Admission").

The Examiner rejects Claims 76, 80, 87 and 92 for allegedly lacking enablement within the Specification. Office Action, page 3. The Applicants respectfully disagree. However, in order to expedite prosecution, Claims 76, 80, 87, and 92 are now amended to include the phrases "*in situ* or *in vivo*" and "wherein said cells comprise tumor cells; wherein said tumor cells are undergoing neovascularization."

Present Claim 76 is directed to the subject matter which the Examiner admits is enabled. As such, the rejection should be withdrawn with respect to Claim 76. For the reasons discussed below, the rejections should also be withdrawn for the other pending Claims as well.

B. New Claims 76, 80, 87 and 92 Recite "*in situ* or *in vivo* imaging of a tumor neovasculature in an individual" As Stated Within The Examiner's Enablement Admission

New Claims 76, 80, 87 and 92 each provide the following phrase: "A method of *in situ* or *in vivo* imaging, comprising providing cells, ... wherein said cells comprise tumor cells, wherein said tumor cells are undergoing neovasculature." As such, per the Examiner's Enablement Admission, that these elements within new Claims 76, 80, 87 and 92 are enabled is not in dispute.

C. New Claims 76, 80, 87 and 92 Recite "administration a chimeric polypeptide" As Stated Within The Examiner's Enablement Admission

New Claims 76, 80, 87 and 92 each provide the following phrase "...providing ... a chimeric polypeptide...administering said chimeric polypeptide to said cells." As such, per the Examiner's Enablement Admission, that these elements within new Claims 76, 80, 87 and 92 are enabled is not in dispute.

D. New Claims 76 and 80 Recite "bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1" As Stated Within The Examiner's Enablement Admission

New Claim 76 provides the following phrase "...wherein said chimeric polypeptide comprises an illumination domain, and a target recognition domain; wherein said illumination domain comprises a luciferase protein; wherein said target recognition domain comprises an RGD sequence; wherein said RGD sequence is SEQ ID NO: 1." As such, per the Examiner's Enablement Admission, that these elements within new Claim 76 are enabled is not in dispute.

New Claim 80 provides the following phrase "wherein said chimeric polypeptide comprises an illumination domain, and a target recognition domain; wherein said illumination domain comprises a bioluminescent polypeptide; wherein said target recognition domain comprises an RGD sequence; wherein said RGD sequence is SEQ ID NO: 1." As such, per the Examiner's Enablement Admission, that these elements within new Claim 80 are enabled is not in dispute.

E. Enablement For RGD Sequence Motifs

The Specification supports enablement of various RGD sequence motifs. A difference between new Claims 87 and 92 and the Examiner's Enablement Admission is that these Claims are not limited to RGD motifs comprising SEQ ID NO: 1. The Specificaiton supports the use of RGD sequences beyond SEQ ID NO: 1. For example, the Specification, at page 15, lines 20-25, incorporate references pertaining to the application of various RGD sequences within empirical settings.

Furthermore, the Examiner has not provided evidence that other RGD sequence motifs will not work as claimed in view of the knowledge in the art. The Applicants are

not claiming "any" sequence having the amino acids RGD. Rather, the Applicants are claiming RGD motifs. To sustain the rejection, the Examiner must provide evidence that the range of RGD motifs described in the Specification and known in the art would not work with the invention as claimed. For example, the Examiner has not provided evidence that a skilled artisan would be unable to select components that will function with the range of RGD motifs described in the Specification and known in the art.

F. Enablement For Providing Cells Comprising Tumor Cells

The Specification supports enablement of cells comprising tumor cells. The Examiner appears to suggest that Claims 76, 80, 87 and 92 are allegedly not enabled for providing cells comprising tumor cells having the recited properties. Office Action, page 3. The Examiner has stated that the Specification is enabling for cells having the claimed properties. Therefore, it appears that the Examiner's concern relates to cells comprising other cells. Example 1 of the Specification provides a nude mouse with an orthotopic tumor. The mouse of Example 1 inherently provides both tumor and non-tumor cells. If the Specification is enabled for the recited tumor cells, it is unquestionably enabled for cells comprising such tumor cells (*e.g.,* such tumor cells in a mixture or a tissue). As such, new Claims 76, 80, 87 and 92 are enabled for providing cells comprising tumor cells.

G. Enablement For Providing An Imaging Agent

The Specification supports enablement of providing an imaging agent. The Examiner appears to suggest that Claims 76, 80, 87 and 92 are allegedly not enabled for providing an imaging agent. Office Action, page 3. The Examiner's position is contradicted by the Examiner's Enablement Admission wherein a bioluminescent polypeptide is provided within an imaging system. Imaging a bioluminescent polypeptide, per the claims, within an in vivo or in situ setting utilizes administration of an imaging agent. The Examiner is directed to the Specification at page 18, lines 23-31 and page 19, lines 1-3 which thoroughly discuss the use of bioluminescent polypeptides and corresponding imaging agents. The Examiner has provided no evidence that one skilled in the art would be unable to match an appropriate imaging agent with the claimed

bioluminescent polypeptide (which themselves, the Examiner admits are enabled). As such, new Claims 76, 80, 87 and 92 are enabled for providing an imaging agent.

H. The Examiner's Arguments

The Examiner provides numerous arguments regarding the enablement of Claims 76-98. However, the presented arguments do not identify the Claims to which they are directed. For example, the Examiner states "the specification fails to provide any guidance as to how to make and how to use any 'chimeric molecule' for *in vitro* or *in vivo* imaging of any cell, comprising providing any agent;" Office Action, page 3; "Applicant has not provided sufficient biochemical information that distinctly identifies 'any cells' possess or are suspected of possessing polypeptides comprising RGD motifs." Office Action, page 4; "Applicant has not provided sufficient biochemical information that distinctly identifies such... 'chimeric molecule' comprises a luciferin protein or any RGD sequence other than the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO: 1;" Office Action, page 4; "RGD sequence is the primary site of recognition by integrins that are expressed on tumor cells and are responsible for tumor invasion. Therefore, there is insufficient direction and guidance as how the method for *in vitro*, *in situ* or *in vivo* imaging of any cell will be accomplished with the RGD-motif-comprising polypeptide;" Office Action, page 4; "Therefore, there is insufficient direction or objective evidence as to how to make and to how to use any chimeric molecule comprising RGD motif-comprising polypeptide which can be used for in situ or in vivo imaging of tumor neovasculature for the number of possibilities associated with the myriad of direct and indirect effects associated with various 'chimeric molecule' and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims;" Office Action, pages 4-5; "In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the Specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention;" Office Action, page 5.

The Applicants disagree with the Examiner. However, in view of the Applicants' Claim amendments, these rejections are rendered moot. The Examiner is directed to the discussion in Sections III A-G as the basis for enablement of the present Claims.

I. Enablement Conclusion

New Claims 76, 80, 87 and 92 (and corresponding dependent claims) are enabled within the Specification. A comparison of new Claims 76, 80, 87 and 92 and the Examiner's Enablement Admission reveal very few differences. These differences are specifically addressed above, and specific Specification support identified. As such, the Applicants request these rejections be withdrawn or that the Examiner provide evidentiary support for the rejections.

IV. New Claims 76-98 Do Not Lack Written Description

In view of the Applicants' Claim amendments, these rejections are rendered moot. For the reasons discussed in Section III A-G regarding enablement, proper written description support for present Claims 76-98 is provided in the Specification.

V. New Claims 76-98 Are Non-Obvious

The Examiner states "Claims 76-98 are rejected under 35 U.S.C. 103(a) as being obvious over ('135 patent), in view of ('476 patent) and further in view of ('084 patent)." The Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143. The Examiner fails to present a *prima facie* case of obviousness.

A. There Is No Reasonable Expectation Of Success

There was no reasonable expectation of success that combining the '135 patent with the '476 patent and '084 patent in the manner suggested by the Examiner would result in Claims 76-98. The Examiner argues, "From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention." Office Action, page 8. However, the Examiner simultaneously emphasizes in the 35 U.S.C. §112 rejections that prior art involving RGD sequences is unpredictable. In particular, the Examiner states, "there is insufficient guidance as to which amino acid segments within the polypeptide can be unique and retain a distinct functional capability of 'RGD motif-comprising polypeptide.' Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute." Office Action, page 4. The Examiner further argues that RGD related art is unpredictable with the statement, "Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid fragment can retain the functional capabilities of the RGD motif-comprising polypeptide requires knowledge of, and guidance with regard to, which segments in the polypeptides sequence contribute to its function." Office Action, page 4. In addition, the Examiner purports, "*Minor structural differences among structurally related compounds or compositions can result in substantially different biological activities*. Therefore, structurally unrelated compounds comprising any 'RGD sequence' *would be expected to have greater differences in their activities*." (emphasis provided) Office Action, page 4.

Combination of the '135 patent with the '084 patent with the technique presented in the '476 patent would require that amino acid sequences be combined with alternate amino acid sequences resulting in the creation of a chimeric molecule. According to the Examiner, this is a highly unpredictable endeavor. Thus, the Examiner's positions in the §112 and §103 arguments are incompatible. In view of the Examiner's §112 position, the §103 rejection must be withdrawn.

B. There Is No Motivation To Combine The References

Claims 76-98 are non-obvious. A *prima facie* showing of obviousness requires that an Examiner *make a showing* of the teaching or motivation to combine prior art references. In re Dembiczak, 175 F.3d 994, 999 (Fed.Cir. 1999) (emphasis provided). Here, the Examiner states "in the instant case, given the teachings of '476 patent that the tumor RGD-containing peptide binds specifically to a sample of the tumor obtained from the patient and the resultant chimeric protein can be used to detect specific binding proteins which reflect in the presence of specific markers in endothelial cells as taught by the '084 patent wherein such imaging method is a non-invasive and allows the detecting of light-emitting conjugates in mammalian subjects as taught by the '135 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to link the RGD containing peptide (claimed SEQ ID NO: 1) taught by '084 patent with the photoprotein with luminescent properties and such chimeric proteins would be of great value in immunoassay systems taught by the '476 patent and use the resultant chimeric molecule in the methods of imaging taught by the '135 patent." Office Action, page 9.

The Applicants respectfully submit that by making these conclusory statements, the Examiner *has not provided any evidence* as to why a skilled artisan would make the combination; he has only stated what he believes each reference teaches in isolation from the other references and then stated that it would be obvious to combine the elements. In order to support the combination, the Examiner has merely relied on the level of skill in the art. This is not permissible. Such unsupported statements are exactly what the Federal Circuit in *In re Rouffet*, 149 F.3d 1350 (Fed.Cir. 1998) sought to prevent. The Federal Circuit stated:

> The Board did not...explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness."

To properly support the rejection, the Examiner must provide concrete evidence (*e.g.*, statements from the prior art, other references, a declaration attesting to the Examiner's personal knowledge, etc.) of a motivation to combine. Without such evidence, the rejection must be withdrawn.

CONCLUSION

All grounds of rejection of the Office Action of September 24, 2003 have been addressed and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's new claims should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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